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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/020,634

12/14/2001

Ronenn Roubenoff

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EXAMINER

KWON, BRIAN YONG S

ART UNIT

PAPER NUMBER

1614

MAIL DATE

DELIVERY MODE

10/05/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

# Office Action Summary

Application No.

10/020,634

Applicant(s)

ROUBENOFF ET AL.

Examiner

Brian S. Kwon

Art Unit

1614

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 09 July 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-13 and 48-71 is/are pending in the application.
- 4a) Of the above claim(s) 10,51-53,56-58,61-63 and 69-71 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-9,11-13,48,49,54,55,59,60,65,67 and 68 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- |                                                                                                            |                                                                                         |
|------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____                                                |

## DETAILED ACTION

### *Applicants Response to Election of Species Requirement Acknowledged*

1. Applicant's election, without traverse, with 5-methyl-tetrahydrofolate and ibuprofen as the elected species is acknowledged. Claims 1-9, 11-13, 48-49, 54-55, 59-60, 65-65 and 67-68 read on the elected species.

### *Status of Application*

2. Acknowledgement is made of applicant's filing of an amendment on 10/25/06. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. By the amendment, claims 1-4 and 11-13 have been amended and claims 48-71 have been added.
3. Claims 1-9, 11-13, 48-49, 54-55, 59-60, 65-65 and 67-68 are currently pending for prosecution on the merits.
4. Applicant's amendment changing the scope of the invention to the combination of a cobalamin, a reduced folate such as 5-methyl-tetrahydrofolate and ibuprofen necessitated the new ground(s) of rejection presented in this Office action.
5. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-9, 11-13, 48-49, 54-55, 59-60, 65-65 and 67-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muller et al. (US 6011040) in view of Rabinoff (USP 5716941) and Horrobin et al. (USP 5603959), and further in view of Smith et al. (WO 98/19690) and Bailey et al. (USP 5997915).

Muller teaches a composition comprising reduced folate compound (i.e., 5-formyl-(6S)-tetrahydrofolic acid, 5-methyl-(6S)-tetrahydrofolic acid, 5,10,methylene-(6R)-tetrahydrofolic acid, 5,10,methenyl-(6R)-tetrahydrofolic acid, 10-formyl-(6R)-tetrahydrofolic acid, 5-formimino-(6S)-tetrahydrofolic acid or (6S)-tetrahydrofolic acid) together with vitamin B (i.e., vitamin B12), wherein an amount of said reduced folate compound is in dose range between

Art Unit: 1614

0.001mg and 1000mg, and an amount of said vitamin B12 is in dose range of 0.001mg and 0.5mg (column 2, lines 19-25; column 3, lines 9-21 and lines 30-40; Example 10; claims 5, 19-20). Muller also teaches that tetrahydrofolates or its derivatives are known to be useful in the treatment of various conditions including anomalies of the homocystein level (e.g., cardiovascular disease and neural tube deficiencies) and autoimmune diseases such as rheumatoid arthritis (column 1, lines 14-17 and 33-34).

Rabinoff teaches use of a methyl donor compound such as methylcobalamin or cyanocobalamin alone or in combination with other known methyl donor compound such as 5-methyl tetrahydrofolic acid and betaine that is useful for the treatment of immunological disorder including autoimmune disease (e.g., rheumatoid arthritis, myocarditis, glomerulonephritis, etc...) and HIV infection (column 3, lines 44-45; column 4, lines 24-27; column 4, line 65 through column 5, line 17).

Horrobin is being provided as a supplemental reference to demonstrate the routine knowledge in using NSAID such as ibuprofen in the treatment of rheumatoid arthritis.

Smith teaches a composition comprising (i) folic acid, betaine and vitamin B12 or (ii) folate or folate derivatives (e.g., tetrahydrofolic acid, 5,10-methylenetetrahydrofolate, 5-methyltetrahydrofolate, 5,10-methylenyltetrahydrofolate, 5-formyltetrahydrofolate, etc...), betaine and vitamin B12, wherein said composition can be prepared in single fixed combination such as single tablet or single capsule (page 4, line 34 thru page 5, line 20; page 10, lines 3-6; page 11, lines 3-9; Example 1; claims 25 and 27). Smith also expressly teaches that (i) the folic acid or folate or derivatives is employed in a weight ratio to vitamin B12 of within the range from about 0.1:1 to about 50:1 and preferably from about 0.2:1 to about 25:1 (column 6, lines 5-8); and (ii)

Art Unit: 1614

the folic acid or folate or derivative or betaine is employed in daily oral doses within the range from about 0.1 to about 100mg, and vitamin B12 is employed in daily oral doses within the range from about 0.001 mg to about 10mg (column 6, lines 41-47).

Bailey teaches the use of the reduced folates as the improved source of folic acid due to their characteristic of natural isomers (which is chemically identical to the most abundant natural forms) and more uniform absorption (column 5, line 24 thru column 6, line 2 and column 6, line 65 thru column 7, line 18). Bailey discloses that the reduced folates would provide the improved alternative for those who may have inadequate response to oral folic acid.

The teaching of Muller differs from the claimed invention in (i) the combination of cobalamine, 5-methyl-tetrahydrofolate and ibuprofen, further comprising betaine and (ii) the specific ratio of the folate compound and the cobalamin is 125:1, (ii).

Above references in combination make clear that cobalamine, 5-methyl-tetrahydrofolate, ibuprofen and betaine have been individually used for the treatment of rheumatoid arthritis. It is obvious to combine two compositions each of which is taught by prior art to be useful for same purpose; idea of combining them flows logically from their having been individually taught in the prior art. The combination of active ingredient with the same character is merely the additive effect of each individual component. *See In re Kerkhoven, 205 USPQ 1069 (CCPA 1980).*

With respect to the specific ratio of the folate compound and the cobalamin or the determination of dosage amounts of betaine, those of ordinary skilled in the art would have been readily optimized effective dosage ratio or dosage amounts in light of Muller who teaches the range of amounts of the reduced folate compound and cobalamin (vitamin B12) in said

Art Unit: 1614

composition and Smith who teaches overlapping dosage amounts of betaine in said composition. One having ordinary skilled in the art would have expected as taught by Muller and/or Smith that said composition could be formulated in the ratio of the reduced folate to cobalamin between 1:1 (when the lower limit of the reduced folate (e.g., 0.001mg) is compared to the lower limit of the cobalamin (e.g., 0.001mg)) to 1:2000 (when the upper limit of the reduced folate (e.g., 1000mg) is compared to the upper limit of the cobalamin (e.g., 0.5mg)) or the claimed dosage amounts of betaine. Based on Muller and/or Smith, one having ordinary skilled in the art would have been able to arrive at the claimed ratio or the dosage amounts without undue amount of experimentation. Thus, the references in combination make obvious the instant invention.

One having ordinary skilled in the art at the time of the invention was made would have recognized in light of the cited references combination that the reduced folates having similar activity as the folate or folic acid in combination with cobalamin would provide similar activity in treating rheumatoid arthritis or improving condition of symptom of rheumatoid arthritis. Furthermore, one having ordinary skilled in the art would have expected as taught by Bailey that the substitution of folate with the reduced folate (i.e., 5-formyl-(6S)-tetrahydrofolic acid, 5-methyl-(6S)-tetrahydrofolic acid, 5,10-methylene-(6R)-tetrahydrofolic acid, 5,10-methenyl-(6R)-tetrahydrofolic acid, 10-formyl-(6R)-tetrahydrofolic acid, 5-formimino-(6S)-tetrahydrofolic acid or (6S)-tetrahydrofolic acid) would provide advantage to those for whom folic acid bioavailability is poor and those who concerns for possible adverse effects. Thus, one would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

With respect to the specific daily dosage amounts of the reduced folate and cobalamin, one would have been readily optimized effective dosage amounts in light of Muller who teaches the reduced folate compound in dose range of 0.001mg and 1000mg, vitamin B12 in dose range of 0.001mg and 0.5mg, and the optimum dosages in therapy vary between 0.1mg and 100mg per day, particularly between 0.5mg and 5 mg per day. One would have been motivated to determine dosage amounts having optimum therapeutic index of the composition.

With respect to "chondroprotective effect" of the said composition, such property or feature is not limiting to the interpretation of the composition claim. Even if the examiner gives a patentable weight to such property, such property is considered to be the expected feature of the claimed composition when the ratio of said reduced folate and said cobalamin is in 125:1. Therefore, Muller makes obvious the instant invention.

Although the instant claims use the different name for the said ingredient than those taught in the cited references, these references are particularly pertinent and relevant because all the claimed species and their roles are well taught in the cited reference. Thus, one would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

### ***Conclusion***

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).



Art Unit: 1614

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. No Claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system,

Application/Control Number: 10/020,634

Page 9

Art Unit: 1614

see <http://pair-direct.uspto.gov> Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Brian Kwon

**Primary Patent Examiner**

**AU 1614**

A handwritten signature in black ink, appearing to be 'B. Kwon', followed by a long horizontal line extending to the right.